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Sub–nanometre metal clusters for catalytic carbon–carbon and carbon–heteroatom cross–coupling reactions

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A. Leyva–Pérez[a]

Catalytic cross–coupling reactions are fundamental transformations in modern organic synthesis. Traditionally based on single–atom transition metal complex catalysts, the use of sub–nanometre metal clusters with enhanced redox and coordinating properties may lead to more efficient catalysts. Recent developments and potential new directions of catalytic sub–nanometre metal clusters for cross–coupling reactions are here briefly discussed.

Introduction

Modern organic synthesis can only be understood with the advent of metal–catalysed cross–coupling reactions, which have facilitated the synthesis of industrially–relevant organic building blocks, fine chemicals, pharmaceuticals, and otherwise unsurmountable synthetic natural products.

Single–atom Pd, Ni and Cu catalytic complexes, among others, are the basis of these advancements, since they show an extraordinary activity and versatility for a plethora of carbon–carbon (C–C) and carbon–heteroatom (C–Het) cross–coupling reactions.[1] In–depth mechanistic studies have unveiled that the coupling reaction generally proceeds by an early oxidation of the metal site, to form a new organometallic species with one of the reactants that, after further substrate coordination and orientation, suffers a final reduction in the metal site to form the coupling product and re–starts the catalytic cycle.[1a] In most cases, the feasibility of the redox events dictates the rate and scope of the coupling. With this in mind, the design of metal structures able to facilitate the redox processes and, at the same time, conveniently manage the reactivity of the substrates on the catalytic site during the mechanistic manifold, will, in principle, give a chance to find more efficient catalysts for cross–coupling reactions.

Sub–nanometre metal clusters (MCs) are structures with typically 2 to <15 metal atoms that still preserve molecular–like electronic properties, in contrast to metal nanoparticles (NPs).[2,3] Either composed exclusively by metal–metal bonds, or with bridging anions or ligands, MCs have well–defined high occupied and low unoccupied molecular orbitals (HOMO and LUMO, respectively), with an energy and shape that easily varies with atomicity, topology and electronic environment of the MC. Indeed, the simple addition of removal of a single metal atom in the cluster, or the change from a 2D to a 3D structure for a given atomicity, provokes a dramatic change in the electronic properties of the MC.[2]

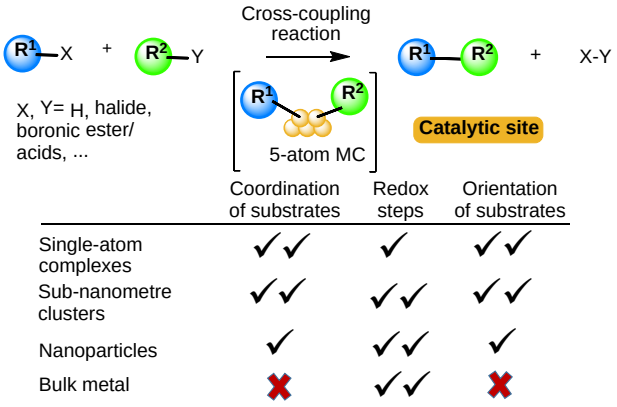

Figure 1 Schematic representation of cross–coupling reactions, summary of the more relevant properties of metal catalysts inherent to the catalytic process, and model of a 5–atom metal cluster after substrate coordination and oxidative addition.

Figure 1 shows a basic scheme of the inherent properties needed for a metal species to catalyse a cross–coupling reaction, which includes coordination and activation of the substrates, redox switch, and convenient orientation of the activated reagents to form the final coupling product. While single metal–atom complexes are very efficient to activate and orientate the substrates,[1b] MCs share and delocalised electron density throughout all metal atoms, thus redox process are in principle favoured in the latter, at least when ligands do not play an active redox role or enable significantly electronic delocalization in the metal complex. The conceptual (and physical) extension of this argument reaches a maximum in metal NPs and bulk metals, where a complete electronic

[a] Instituto de Tecnología Química, Universitat Politècnica de València–Consejo Superior de Investigaciones Científicas, Avda. de los Naranjos s/n, 46022, Valencia (Spain). E–mail: anleyva@itq.upv.es.

delocalization occurs. However, substrate managing is generally less efficient on metal surfaces, and this explains why bulk metals are comparatively inactive for these reactions.

Metal NPs, with unsaturated atoms in corners, vertexes and steps, do allow substrate coordination and activation, and indeed show significant catalytic activity in cross–coupling reactions.[3] A paradigmatic case is the Au NP–catalysed Sonogashira coupling: The Au^{+} to Au^{3+} formal $2e^{-}$ oxidation, expected for a single–atom Au catalyst, is energetically prohibitive in the absence of strong sacrificial oxidising agents and, accordingly, Au^{+} salts and complexes are poor catalysts for the C–C coupling; however, in clear contrast, Au NPs are good catalysts,[3b] and mechanistic studies confirm the much easier oxidative addition of the aryl halide on the Au NP through Au–Au atom cooperation.[3c,d] However, NPs still lack well–defined molecular orbitals and metal atom homogeneity for an optimal electronic and steric control of the substrates.[3e]

Catalytic sub–nanometre metal clusters in cross–coupling reactions.

Recent developments.

MCs, between single–atoms and NPs, can finely adjust electronics of the valence orbitals directly involved in the catalytic reaction for substrate activation, redox steps and final coupling, fulfilling the requirements for an efficient catalytic cross–coupling reaction. Recent literature points to this direction.

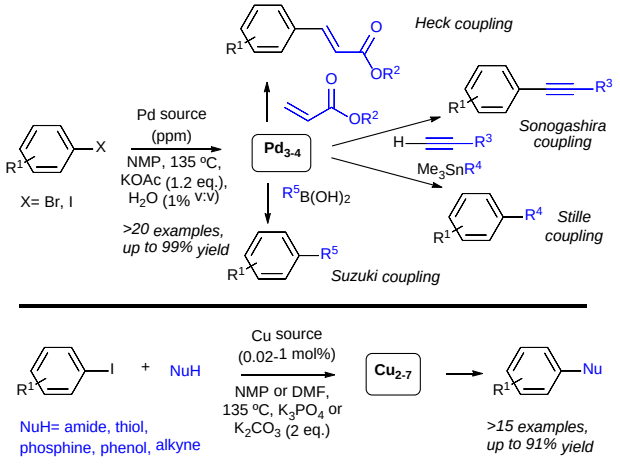

Figure 2 C–C and C–Het cross–coupling reactions catalysed by in–situ formed, ligand–free Pd (top) and Cu (bottom) MCs.

Figure 2 shows that $Pd_{3–4}$ clusters catalyse representative C–C cross–coupling reactions of aryl iodides and bromides, such as the Heck, Suzuki, Sonogashira and Stille reaction, with close to a million of turnover numbers (TONs) and turnover frequencies (TOFs).[4a] The catalytically active $Pd_{3–4}$ clusters are formed in–situ in part–per–million (ppm) amounts from either salts, complexes or NPs. Figure 2 also shows that $Cu_{2–7}$ clusters are formed in a similar way, to catalyse the C–N cross–coupling Goldberg reaction in ppm amounts.[4b] The $Cu_{2–7}$ catalysts are also active for C–P, C–O and C–C cross coupling bond–forming reactions, which illustrates the versatility of the Cu clusters after aryl halide activation. Both Pd and Cu catalytic MCs clearly exceed the catalytic activity of the corresponding NPs, however, it must be noticed that these MCs are still far from the activity of metal complexes, particularly with aryl chlorides.[4c]

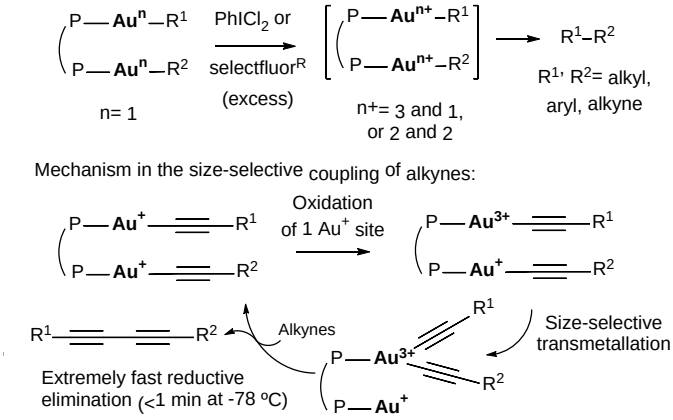

Figure 3 Oxidative cross–couplings with phosphine–bridged Au_2 catalysts and mechanism of the coupling of alkynes.

The absence of ligands can be considered an advantage from a practical and economical point of view, however, ligands are essential for some catalytic MCs. For instance, Figure 3 shows that phosphine bridged Au_2 complexes bear unique catalytic activity for different oxidative coupling reactions, including the biaryl coupling, the homo– and hetero–coupling of alkynes, and the heteroarylation of alkenes with boronic acids.[5a–c] For the former two, an intermediate mixed–valence Au^{+}–Au^{3+} bimetallic complex is proposed,[5b–c] while for the latter, a Au^{2+}–Au^{2+} dimer seems more plausible.[5a] In both cases, the co–operation of the two Au sites with the assistance of fluoride anions is key for the coupling, while the phosphine ligands preserve the structure of the Au_2 intermediate after oxidation of the Au^{+} sites with extremely strong oxidasing agents. In particular, the size–selective coupling of alkynes, whose mechanism is also shown in Figure 3, occurs after selective transmetallation of an alkyne from the Au^{+} to the Au^{3+} site, which finally gives the bisalkyne product by extremely fast reductive elimination. Group 11 metal NPs and Cu complexes can be very active for the homocoupling of alkynes, but non selective.[5d]

C–H activation is at the forefront of research in organic chemistry, since they avoid previous functionalization of the substrates. MCs with well–defined atom positions might selectively activate and couple a particular C–H bond in some molecules and, indeed, the Au_2–catalysed alkyne coupling is a particular case of selective C–H cross–coupling.[5c] Perhaps more challenging and with wider scope, Figure 4 shows the aerobic coupling of arenes catalysed by in–situ formed Pd_2 cluster complexes, an illustrative example of selective C–H activation by catalytic metal co–operation.[6] The biaryl product is relevant to polymer production, and kinetic studies, including isotopic experiments, confirm the participation of 2 Pd atoms in the

rate–determining step of the coupling.[6b] Au NPs catalyse this biaryl coupling with low efficiency.[6c]

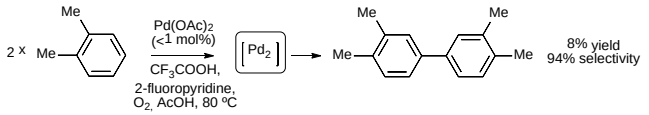

Figure 4 Biaryl C–H cross–coupling with Pd_2 intermediates.

Future directions.

Ligand–free MCs. These MCs expose their localized valence orbitals directly towards the incoming reactants, and with tunable redox properties, they are potential catalysts for a variety of cross–coupling reactions, as shown in Figure 2. However, up to know, catalysis with ligand–free MCs is based on speciation and maximization from a cocktail of catalytic mixtures,[7] since the synthesis of well–defined ligand–free MCs is still in its infancy.[8] The recent synthesis and characterisation by X–ray diffraction crystallography (XRD) of a quasi–linear, mixed–valence Pd_4 MCs supported on a non–coordinating MOF can be considered as a representative example of perfectly defined "ligand–free" MC with catalytic properties.[9] Despite cocktail catalysts are operative, the synthesis of well–defined ligand–free MCs should lead to new MC–catalysed cross–coupling reactions based on a "catalyst–to–reaction" rather than on a "reaction–to–catalyst" approach.

Ligand–stabilised MCs. They have the advantage of being perfectly characterised by techniques such as XRD and nuclear magnetic resonance (NMR), however, they decompose as soon as the ligands are significantly perturbed, which tends to occur during the catalytic process.[9] Robust enough MC structures to cope with the cross–coupling reaction conditions, such as in the bridging phosphine MCs shown above, could catalyse cross–coupling reactions.

Solid–supported MCs. They have been reported as catalysts for oxidations, dehydrogenations and addition reactions, [10] but not for cross–couplings. If active, these supported MCs can be used as recyclable heterogeneous catalysts once leaching issues are avoided.[11] However, much precise synthetic techniques for their synthesis must be developed.[9,12] since only soft–landing techniques allows so far well–defined supported MCs.[13]

Conclusions

MCs with suitable electronic and steric properties efficiently catalyse C–C and C–Het cross–coupling reactions. Once well–defined ligand–free MCs are prepared, and the role of supports and ligands is understood, the design of MCs with different atomicity, geometry, oxidation states and even different metals in the same cluster, should lead to efficient catalyst for known and new cross–coupling reactions, including C–H activation.

Conflicts of interest

There are no conflicts to declare.

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